REMARKS

In the Action, pending claims 1-5 and 77 were variously rejected under 35 U.S.C. §112, first paragraph, for assertedly lacking written description and enablement, and under 35 U.S.C. § 103(a) as assertedly obvious in view of Banks et al. (*Peptides*, 17:305-11, 1996) (hereinafter "Banks") further in view of Borges (*Eur. J Pharmacology* 269:243-48, 1994) (herinafter "Borges") and Caro et al. (*Lancet* 348:159-61,) (hereinafter "Caro"). Reconsideration is requested in light of the following remarks.

I. The Subject Matter of the Claims

The subject matter of the claims relates, in general, to methods of modulating the transport of leptin across the blood-brain barrier (BBB).

II. Support for Amendment to the Claims

Support for the amendment to the claims is found throughout the specification. For example, page 5, lines 3-12 teaches that epinephrine is contemplated for use in the methods of the invention. Page 10, line 1, to page 11, line 15 describes leptin analogs contemplated for use in the methods of the invention and page 11, lines 17-30 describe fragments of leptin peptides contemplated for use in the invention.

IV. Patentability Argument

A. The Rejection of Claims 1-5 and 77 Under 35 U.S.C. §112, First Paragraph, for Lack of Enablement Should Properly Be Withdrawn

The Examiner maintained the rejection of claims 1-5 and 77 under 35 U.S.C. §112, first paragraph, as assertedly not being enabled because, according to the Examiner, Applicant has not enabled transport of all leptins, variants, analogs, leptin fusion proteins, chemical derivatives and fragments thereof, across the BBB.

Claims 3 and 4 have been amended to include reference to leptin analogs and leptin fragments contemplated for use in the method of the invention. The claim also recites that the leptins are biologically active and may be transported across the blood brain barrier (BBB).

Applicant submits that all of the leptins recited in the claims are enabled in the specification and in the art. The specification teaches, at page 9, line 11, to page 12, line 8, that certain residues in the leptin proteins are more conserved throughout species and that other residues, such as those residues recited in the claims and in the specification, are more amenable to substitution. The specification also teaches fragments of leptin (page 11, lines 17-30) that are contemplated by the invention. Additionally, U.S. Patents 6,734,160 and 6,471,956 (submitted with the response of June 30, 2005) describe and claim leptin fragments and analogs. These fragments are described in terms of where the leptin protein may be truncated or substituted (see U.S. Patent 6,471,956, col. 18 to col. 20).

The specification also teaches, at page 12, line 15, to page 16, line 5, methods of making leptin fusion proteins and leptin derivatives comprising chemical moieties (e.g., PEG). The generation of fusion proteins and attachment of chemical moieties to a protein is routine in the art (see pages 12 -16 of the specification) and does not place an undue burden on a person of ordinary skill to make a chemical derivative of a leptin recited in the claims.

Further, the art describes methods to determine if a leptin sequence has biological activity, by measuring leptin binding to leptin-specific antibodies, leptin competition assays, and leptin receptor binding assays. Moreover, the specification teaches methods to measure leptin transport across the BBB (see Example 1, page 17). A worker of ordinary skill in the art taught leptin analogs and fragment in the specification and in the art would require only routine experimentation to determine the biological activity of the leptins and to determine transport of

the leptin across the BBB. As such, a worker of ordinary skill does not face an undue burden in making leptin analogs or fragments thereof and using the leptins in the method of the invention.

Applicant has taught how to make the leptins recited in the claims and taught methods to determine the biological activity of a leptin protein and methods for measuring transport across the BBB. Further, the specification teaches, and it is well-known in the art, how to make chemical derivatives of a protein and how to generate fusion proteins of a particular protein of interest. Therefore, Applicant has taught a worker of ordinary skill in the art to make and use the methods of the invention, and a person of ordinary skill would only have to use routine experimentation to repeat these methods.

For these reasons, the Examiner's rejections under 35 U.S.C. §112, first paragraph, enablement, should be withdrawn.

B. The Rejection of Claims 1-5 Under 35 U.S.C. §112, First Paragraph, Written Description Should Properly Be Withdrawn

The Examiner maintained the rejection of claims 1-5 and 77 under 35 U.S.C. §112, first paragraph, as allegedly lacking written description, asserting that Applicant has not described all leptin variants and fragments encompassed by the claims. Applicant respectfully disagrees.

As discussed above, claims 3 and 4 have been amended to recite leptin analogs and leptin fragments contemplated for use in the method of the invention. The claim also recites that the leptins are biologically active and may be transported across the blood brain barrier (BBB).

Applicant stated previously that biologically active leptin fragments, variants, consensus sequences and the like are described in the specification and well-known in the art (See U.S. Patents 6,350,730, 6,309,853, 6,734,160, 6,429,290 and 6,471,956). The specification

describes, and the claims enumerate, which leptin sequences are preferred in a leptin fragment polypeptide for use in the method of the invention, and which amino acids can be changed, and to which amino acids they can be changed, to arrive at a consensus leptin sequence (page 10, line 1, to page 12, line 8).

Further, the specification at page 12, line 9, to page 16, line 5, describes chemical modifications common in the art and contemplated as chemical modification of the leptins in the claims, including leptin analogs or fragments of leptin. For example, the specification describes that the leptins useful in the invention may be modified using water soluble polymers, such as polyethylene glycol, dextran, polyvinyl alcohol, and many other chemical moieties well-known in the art (page 13, lines 6-14). As stated previously, what is well-known to one of ordinary skill in the art need not be disclosed in detail in the specification ((Hybritech Inc.v Monoclonal Antibodies Inc., 802 F. 2d 1367 (Fed. Cir. 1986)). Chemical moieties useful for making modified polypeptides are well-known in the art as are methods for making chemically modified polypeptides and may be readily attached to either a full-length leptin or a fragment or analog of leptin that is described in the specification.

Given the description in the specification of leptin, leptin fragments, leptin analogs and consensus sequences, and chemical moieties that may be attached to any of the contemplated leptins, and the general skill and knowledge in the art of making any of these leptins, one of ordinary skill in the art would recognize that Applicant was in possession of the invention, including chemically modified leptins and fragments thereof, at the time of filing.

For the reasons set out above, the rejection of claims 1-5 under 35 U.S.C. §112, first paragraph, written description, should be withdrawn.

C. The Rejection of Claims 1-5 Under 35 U.S.C. §103(a), Should Properly Be Withdrawn

The Examiner maintained the rejection of claims 1-5 and 77 under 35 U.S.C. §103(a) as assertedly obvious over Banks (*Peptides* 1996, 17:305-311), in view of Borges (*Eur. J Pharmacol.* 1994, 269:243-48), further in view of Caro (*Lancet* 1996, 348:159-161). The Examiner asserts that because Banks and Caro assertedly teach that leptin requires transport across the BBB, and Borges assertedly teaches that epinephrine increases non-specific permeability of molecules across microvascular cells in vitro, a worker of ordinary skill in the art would be motivated to combine the teachings of Banks, Caro and Borges to arrive at the present invention. Applicant respectfully disagrees.

The nature of the Examiner's rejection implies that any agent that increases the permeability of the BBB would have a similar effect as epinephrine. Applicant agrees that Borges discloses that administration of adrenaline (epinephrine) and another adrenergic agonist, phenylephrine, increases the permeability of microvascular endothelial cells to an impermeable solute, exemplified by sodium fluorescein bound to albumin. Borges, however does not test this theory on any other impermeable solute, and neither discloses nor suggests administration of leptin in conjunction with epinephrine to increase leptin transport. Borges also does not suggest that epinephrine can be used to modulate specific transport mechanisms.

Borges teaches that epinephrine is a non-specific permeabilizer of the BBB and likely enhances uptake through a pinocytotic mechanism (page 247, col. 1). Caro and Banks teach that leptin uptake is through a saturable transport mechanism. One of ordinary skill would not expect that an agent that non-specifically disrupted the BBB and enhanced pinocytotic molecule uptake would enhance the specific uptake of leptin. There is certainly no indication in Borges, Banks or

Caro, taken alone or in combination, that epinephrine may enhance specific transport of any molecule across the BBB.

In fact, epinephrine does not promote the transport of all compounds across the BBB. For instance, Banks et al (Brain Res. 899:209-217, 2001, ref C6 on 1449) (hereinafter "Banks C6") analyzed the effects of epinephrine on the transport of leptin as well as TNF-α and insulin, all of which are involved in the regulation of appetite and transported across the BBB by saturable transport mechanisms. Banks showed that epinephrine did not increase the levels of TNF-α or insulin transported across the BBB, but did increase leptin transport across the BBB. Additionally, TNF-α (17kD) and leptin (16 kD) are approximately the same size and would be expected to be transported at similar rates by a non-specific transport mechanism.

Unlike the prediction in Borges and by the Examiner epinephrine does not permeabilize the BBB to all proteins, and the effect of epinephrine on leptin transport is specific for leptin and not other proteins that cross the BBB. Moreover, other compounds that disrupt the BBB similarly to epinephrine do not increase the transport of leptin across the BBB. Administration of the adrenergic agonist phenylephrine, used by Borges to increase BBB permeability, does not increase transport of leptin across the BBB (See Declaration of Banks, Exhibit B). Also, administration of lipopolysaccaride (LPS) which disrupts the BBB did not enhance the transport of leptin across the BBB, but actually inhibited leptin transport across the BBB (Nonaka et al., *Brain Res.* 1016:58-65, 2004) (Exhibit A). Thus, not all the agents disclosed by Borges or in the art that are useful to increase BBB permeability modulate leptin transport across the BBB.

Based on the Examiner's assertion, a worker of ordinary skill in the art would assume that infusion of epinephrine, or any other agent capable of permeabilizing the BBB, would

increase transport of any molecule that could cross the BBB. As stated above, see e.g., Banks C6 and Nonaka et al. (*supra*), that is not the case. Applicants have discovered that administration of epinephrine enhances specific uptake of exogenous leptin across the BBB (see Example 3, pages 20-21 and Table 3, and Banks C6). The disclosure in the application, in view of the art, indicates that the present invention demonstrates the unexpected result that epinephrine specifically modulates leptin uptake through the leptin transport mechanism and does not modulate uptake of all molecules, despite its property as a non-specific permeabilizer of the BBB.

Based on the teachings of Borges that epinephrine is a non-specific permeabilizer of the BBB, there would be no reasonable expectation of success at obtaining the specific transport of leptin as taught in Caro by administering epinephrine. One of ordinary skill would have no motivation to combine the teachings and arrive at the present invention based on the disclosures of Banks, Borges and Caro. Further, the disclosure of Banks C6 and Nonaka et al. (*supra*) teach that epinephrine or other agents that permeabilize the BBB do not necessarily enhance transport of all proteins across the BBB. The specification, however, demonstrates the unexpected results of epinephrine modulation of leptin transport recited in the claimed invention. Therefore, the rejection of claims 1-5 and 77 under 35 U.S.C. §103(a) should be withdrawn.

V. Conclusion

Applicants submit that the application is now in condition for allowance and respectfully request notice of the same.

Dated: December 13, 2006

Respectfully submitted,

By _____

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